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(71) Applicant *(for all designated States except US)*: METAMORPHIX, INC. [US/US]; 1450 South Rolling Road, Baltimore, MD 21227 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: MATZUK, Martin, Matthew [US/US]; 2926 Russett Place West, Pearland, TX 77584 (US). ELVIN, Julia, Andrea [US/US]; 3114 Stanton Street, Houston, TX 77025 (US).

(74) Agents: MANDRAGOURAS, Amy, E. et al.; Lahive & Cockfield, LLP, 28 State Street, Boston, MA 02109 (US).

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(88) Date of publication of the international search report:
18 November 1999 (18.11.99)

(54) Title: GROWTH DIFFERENTIATION FACTOR–9 REGULATORY SEQUENCES AND USES THEREFOR

(57) Abstract

Isolated GDF–9 regulatory sequences are disclosed, as well as methods of using the sequences to modulate tissue–specific expression of genes. The GDF–9 regulatory sequences include, for example, enhancer and promoter elements that naturally drive transcription of GDF–9 in specific tissues. The GDF–9 regulatory sequences can be derived from the untranscribed upstream (e.g., first 10 kilobases) and downstream regions, and transcribed, untranslated regions of a GDF–9 gene.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/07185

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/85 A61K48/00 C12N15/11

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C12N A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE EMBL 'Online! Sequence with accession number aa388141, 25 June 1997 (1997-06-25) MARRA, M. ET AL.: "The WashU-MMMI Mouse EST Project" XP002115952 * Sequence corresponds to nucleotides 2994-3375 of SEQ ID No. 1 * ---	1,2,7-10
X	DATABASE EMBL 'Online! Sequence with accession number AA035964, 27 August 1996 (1996-08-27) MARRA, M. ET AL.: "The WashU-HHMI Mouse EST Project" XP002115953 * Sequence corresponds to nucleotides 2601-2891 of SEQ ID No. 1 * --- -/--	1,2,7-10

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 September 1999	05/10/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Hermann, R

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/07185

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	INCERTI, B. ET AL.: "Structure of the mouse growth/differentiation factor 9 gene" BIOCHIM. BIOPHYS. ACTA, vol. 1222, 1994, pages 125-128, XP000646842 cited in the application * page 125; figs. 1 and 2 *	1-22
Y	GARVER, R.I. ET AL.: "Strategy for achieving selective killing of carcinomas" GENE THERAPY, vol. 1, 1994, pages 46-50, XP000569793 * whole disclosure *	1-22
Y	WO 97 19180 A (GLAXO GROUP LTD.) 29 May 1997 (1997-05-29) * page 5-9; claims 2-6 *	1-22
Y	WO 95 06118 A (BOARD OF REGENTSOF THE UNIVERSITY OF OKLAHOMA) 2 March 1995 (1995-03-02) * pages 5 and 6; claim 1 *	1-21

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Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 99/07185

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9719180 A	29-05-1997	AU 7583996 A	11-06-1997
		AU 7700496 A	11-06-1997
		WO 9719183 A	29-05-1997
WO 9506118 A	02-03-1995	US 5605821 A	25-02-1997
		AU 7671394 A	21-03-1995
		CA 2169941 A	02-03-1995

PATENT COOPERATION TRI TY

by fax and post

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

MANDRAGOURAS, Amy E.
LAHIVE & COCKFIELD,LLP
28 State Street
BOSTON,MA 02109
ETATS-UNIS D'AMERIQUE

FAX NO: ((617) 742-4214

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	13.07.00
Applicant's or agent's file reference MTN-029PC	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US99/07185	31/03/1999	01/04/1998

Applicant
METAMORPHIX, INC. et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

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RETRIEVED: 8/15
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Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Büchler, S Tel.+49 89 2399-8090

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference MTN-029PC	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US99/07185	International filing date *(day/month/year)* 31/03/1999	Priority date *(day/month/year)* 01/04/1998
International Patent Classification (IPC) or national classification and IPC C12N15/85		
Applicant METAMORPHIX, INC. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
01/11/1999	13.07.00
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Surdej. P Telephone No. +49 89 2399 7334

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US99/07185

I. Basis of the r port

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-22 as originally filed

Claims, No.:

1-22 with telefax of 23/06/2000

Drawings, sheets:

1/7-7/7 as originally filed

ALREADY CITED IN THE (220') INT'L SEARCH Rpt.

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

see separate sheet

4. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1,2,7-10
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-22
Industrial applicability (IA)	Yes:	Claims	1-22
	No:	Claims	

2. Citations and explanations

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Reference is made to the following documents:

D1: DATABASE EMBL [Online] Sequence with accession number aa388141, 25 June 1997 (1997-06-25) MARRA, M. ET AL.: 'The WashU-MMMI Mouse EST Project'

D2: DATABASE EMBL [Online] Sequence with accession number AA035964, 27 August 1996 (1996-08-27) MARRA, M. ET AL.: 'The WashU-HHMI Mouse EST Project'

D3: GARVER, R.I. ET AL.: 'Strategy for achieving selective killing of carcinomas' GENE THERAPY, vol. 1, 1994, pages 46-50

D4: WO 97 19180 A (GLAXO GROUP LTD.) 29 May 1997 (1997-05-29)

D5: WO 95 06118 A (BOARD OF REGENTSOF THE UNIVERSITY OF OKLAHOMA) 2 March 1995 (1995-03-02)

D6: INCERTI, B. ET AL.: 'Structure of the mouse growth/differentiation factor 9 gene' BIOCHIM. BIOPHYS. ACTA, vol. 1222, 1994, pages 125-128, cited in the application

Introduction

The application discloses growth differentiation factor-9 regulatory sequences and uses thereof.

Re Item I

Basis of the opinion

1. The amendments filed with the letter dated 23 June 2000 introduce subject-matter which extends beyond the content of the application as filed, contrary to Article 34(2)(b) PCT. The **amendments concern claims 1, 7 and 8 in which "is greater than 261 nucleotides in length"** is added. No basis appears to exist in the application as filed for the amendments proposed since the feature "greater than 261 nucleotides in length" for the isolated polynucleotides claimed was not disclosed.

2. Therefore, the International Preliminary Examination Report is established on the application as originally filed.

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Novelty (Art. 33(1) and (2) PCT)

3. Documents D1 and D2 (ESTs with accession numbers AA388141 and AA035964) have been cited as examples for polynucleotides which are "derived from" a polynucleotide "comprising a GDF-9 regulatory element ...".
Such ESTs anticipate present claims 1, 2 and 7-10 due to the vague definition of the claimed subject-matter (see also point 8).

Inventive step (Art. 33 (1) and (3) PCT)

4. D3-D5 (Garver et al.; WO-A-97/19180; WO-A-95/06118) are cited as examples for solutions to the problem underlying the present invention, i.e. tissue-specific expression of genes.
D3-D5 solve this problem by using regulatory elements of selectively expressed genes.

5. The only systematic difference between the present application and D3-D5 resides in the selection of GDF-9 regulatory elements.

6. D6 (Incerti et al.) discloses the GDF-9 gene structure (Fig.1), the sequence of the entire coding region (exon and intron, Fig. 2), and mentions the selective expression of GDF-9 (page 125, 2nd column, 2nd paragraph).
D6 provides sufficient information and incentive for the skilled person to isolate GDF-9 regulatory element and to use them in an approach similar to the ones of D3-D5.
In addition, from the prior art no particular difficulty appears to exist to provide the solution of the technical problem of the present application. The existence of restricted expression (in germ line) of the GDF-9 gene inferred from D6 together with methods known in the art to characterize regulatory sequences of genes having a restricted expression would have led the person skilled in the art directly

to the subject-matter of the application.

7. No inventive merit can be recognized by the mere presentation of some ill-defined "regulatory elements" of a well-known, selectively expressed gene (claims 1-10), and their use in a well-known method (and related subject-matter, claims 11-22).

Re Item VIII

Certain observations on the international application

8. The terms "comprising" and "derived from" introduce unclarity, especially in combination with description, page 13, line 12, that contemplates constructs with only "50% homology" as covered by the terms of the claim:
first, "50% identity" covers almost unrelated sequences,
second, "50% homology" has no meaning at all. Homologous sequences are sequences which have the same evolutionary origin, but which need not to have any identity at all.

PATENT COOPERATION TREATY

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(PCT Article 36 and Rule 70)

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Date of submission of the demand	Date of completion of this report
01/11/1999	13.07.00
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Surdej, P Telephone No. +49 89 2399 7334

Form PCT/IPEA/409 (cover sheet) (January 1994)

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International application No. PCT/US99/07185

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Drawings, sheets:

1/7-7/7	as originally filed

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see separate sheet

4. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with r gard to novelty, inventive st p or industrial applicability; citations and explanations supporting such statement

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Inventive step (IS)	Yes:	Claims	
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	No:	Claims	

2. Citations and explanations

see separate sheet

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see separate sheet

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D2: DATABASE EMBL [Online] Sequence with accession number AA035964, 27 August 1996 (1996-08-27) MARRA, M. ET AL.: 'The WashU-HHMI Mouse EST Project'

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1. The amendments filed with the letter dated 23 June 2000 introduce subject-matter which extends beyond the content of the application as filed, contrary to Article 34(2)(b) PCT. The **amendments concern claims 1, 7 and 8 in which "is greater than 261 nucleotides in length"** is added. No basis appears to exist in the application as filed for the amendments proposed since the feature "greater than 261 nucleotides in length" for the isolated polynucleotides claimed was not disclosed.

2. Therefore, the International Preliminary Examination Report is established on the application as originally filed.

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Novelty (Art. 33(1) and (2) PCT)

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Such ESTs anticipate present claims 1, 2 and 7-10 due to the vague definition of the claimed subject-matter (see also point 8).

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4. D3-D5 (Garver et al.; WO-A-97/19180; WO-A-95/06118) are cited as examples for solutions to the problem underlying the present invention, i.e. tissue-specific expression of genes.
D3-D5 solve this problem by using regulatory elements of selectively expressed genes.

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D6 provides sufficient information and incentive for the skilled person to isolate GDF-9 regulatory element and to use them in an approach similar to the ones of D3-D5.
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to the subject-matter of the application.

7. No inventive merit can be recognized by the mere presentation of some ill-defined "regulatory elements" of a well-known, selectively expressed gene (claims 1-10), and their use in a well-known method (and related subject-matter, claims 11-22).

Re Item VIII

Certain observations on the international application

8. The terms "comprising" and "derived from" introduce unclarity, especially in combination with description, page 13, line 12, that contemplates constructs with only "50% homology" as covered by the terms of the claim:
first, "50% identity" covers almost unrelated sequences,
second, "50% homology" has no meaning at all. Homologous sequences are sequences which have the same evolutionary origin, but which need not to have any identity at all.

What is claim d is:

1. An isolated polynucleotide comprising a GDF-9 regulatory element derived from a region of a nonhuman GDF-9 gene selected from the group consisting of the first 10 kilobases of DNA immediately 5' of the transcription start site, an intron, and the first 1 kilobase of DNA immediately 3' of the transcription termination site, wherein said isolated polynucleotide is greater than 261 nucleotides in length.

2. The polynucleotide of claim 1 wherein the regulatory element is derived from the first 3.3 kilobases of DNA immediately 5' of the transcription start site of the nonhuman GDF-9 gene.

3. The polynucleotide of claim 1 wherein the regulatory element is derived from the first 300 base pairs of DNA immediately 5' of the transcription start site of the nonhuman GDF-9 gene.

4. An isolated polynucleotide comprising the first 10 kilobases of DNA immediately 5' of the transcription start site of a nonhuman GDF-9 gene.

5. An isolated polynucleotide comprising the first 3.3 kilobases of DNA immediately 5' of the transcription start site of a nonhuman GDF-9 gene.

6. An isolated polynucleotide comprising the region from 3.3 kilobases to 10 kilobases immediately 5' of the transcription start site of a nonhuman GDF-9 gene.

7. An isolated oocyte-specific regulatory element derived from the 10 kilobases of DNA immediately 5' of the transcription start site of a GDF-9 gene, wherein said oocyte-specific regulatory element is greater than 261 nucleotides in length.

8. An isolated testis-specific regulatory element derived from the 10 kilobases of DNA immediately 5' of the transcription start site of a GDF-9 gene, wherein said testis-specific regulatory element is greater than 261 nucleotides in length.

9. The regulatory element of claim 8, wherein said element is derived from the first 3.3 kilobases of DNA immediately 5' of the transcription start site of a GDF-9 gene, and wherein said element causes tissue-specific expression of a gene operatively linked to the element in the testis.

10. The regulatory element of claim 8, wherein said element is derived from the region from 3.3 kilobases to 10 kilobases of DNA immediately 5' of the transcription start site of a GDF-9 gene, and wherein said element downregulates expression of a gene operatively linked to the element in the testis.

11. An expression vector comprising the isolated GDF-9 polynucleotide of any one of claims 1, 4, 5 or 6 operably linked to a gene.

12. The expression vector of claim 11, wherein the gene is a reporter gene.

13. An oocyte containing the polynucleotide of any one of claims 1, 4, 5 or 6.

14. A method for obtaining oocyte-specific expression of a gene, the method comprising transfecting an oocyte with the isolated polynucleotide of claim 1.

15. The method of claim 14, wherein said polynucleotide is operably linked to a gene.

16. A method for obtaining testis-specific expression of a gene, the method comprising transfecting a testicular cell with the isolated polynucleotide of claim 2.

17. The method of claim 16, wherein said polynucleotide is operably linked to a gene.

18. A method for down-regulating the expression of a gene in the testis, comprising transfecting a testicular cell with the isolated polynucleotide of claim 4.

19. A method for identifying tissue-specific regulatory elements for GDF-9 expression comprising, in any order, the steps of:

a) introducing into a cell a first expression vector comprising a portion of the region spanning 1 to10 kilobases immediately 5' of the transcription start site of a GDF-9 gene;

b) introducing into a cell a second expression vector comprising a portion of the region spanning 1 to 10 kilobases immediately 5° of the transcription start site of a GDF-9 gene, wherein the portion differs from that contained in said first expression vector; and

c) comparing expression patterns of said first and second vectors.

20. The method of claim 19, wherein said cell from an oocyte.

21. The method of claim 19, wherein said expression constructs are introduced into said cell via microinjection.

22. The method of claim 19, wherein said expression constructs are introduced into said cell via injection of a transgenic animal.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
MTN-029PC		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US 99/ 07185	31/03/1999	01/04/1998
Applicant		
METAMORPHIX, INC. et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [X] contained in the international application in written form.

   [X] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [X] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [X] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [X] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/07185

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/85 A61K48/00 C12N15/11

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C12N A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE EMBL 'Online! Sequence with accession number aa388141, 25 June 1997 (1997-06-25) MARRA, M. ET AL.: "The WashU-MMMI Mouse EST Project" XP002115952 * Sequence corresponds to nucleotides 2994-3375 of SEQ ID No. 1 * ---	1,2,7-10
X	DATABASE EMBL 'Online! Sequence with accession number AA035964, 27 August 1996 (1996-08-27) MARRA, M. ET AL.: "The WashU-HHMI Mouse EST Project" XP002115953 * Sequence corresponds to nucleotides 2601-2891 of SEQ ID No. 1 * --- -/--	1,2,7-10

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 September 1999	05/10/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Hermann, R

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/07185

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	INCERTI, B. ET AL.: "Structure of the mouse growth/differentiation factor 9 gene" BIOCHIM. BIOPHYS. ACTA, vol. 1222, 1994, pages 125-128, XP000646842 cited in the application * page 125; figs. 1 and 2 *	1-22
Y	GARVER, R.I. ET AL.: "Strategy for achieving selective killing of carcinomas" GENE THERAPY, vol. 1, 1994, pages 46-50, XP000569793 * whole disclosure *	1-22
Y	WO 97 19180 A (GLAXO GROUP LTD.) 29 May 1997 (1997-05-29) * page 5-9; claims 2-6 *	1-22
Y	WO 95 06118 A (BOARD OF REGENTSOF THE UNIVERSITY OF OKLAHOMA) 2 March 1995 (1995-03-02) * pages 5 and 6; claim 1 *	1-21

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Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 99/07185

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9719180 A	29-05-1997	AU 7583996 A	11-06-1997
		AU 7700496 A	11-06-1997
		WO 9719183 A	29-05-1997
WO 9506118 A	02-03-1995	US 5605821 A	25-02-1997
		AU 7671394 A	21-03-1995
		CA 2169941 A	02-03-1995